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Short term memory binding is impaired in AD but not in non-AD dementias

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Running head: STM binding in the differential diagnosis of AD

Abstract

Binding is a cognitive function responsible for integrating features within complex stimuli (e.g., shape-colour conjunctions) or events within complex memories (e.g., face-name associations). This function operates both in short-term memory (STM) and in long-term memory (LTM) and is severely affected by Alzheimer's Disease (AD). However, forming conjunctions in STM is the only binding function which is not affected by healthy ageing or chronic depression. Whether this specificity holds true across other non-AD dementias is as yet unknown. The present study investigated STM conjunctive binding in a sample of AD patients and patients with other non-AD dementias using a task which has proved sensitive to the effects of AD. The STM task assesses the free recall of objects, colours, and the bindings of objects and colours. Patients with AD, Frontotemporal Dementia, Vascular Dementia, Lewy Body Dementia and Dementia associated with Parkinson's Disease showed memory, visuo-spatial, executive and attentional deficits on standard neuropsychological assessment. However, only AD patients showed STM binding deficits. This deficit was observed even when memory for single features was at a similar level across patient groups. Regression and discriminant analyses confirmed that the STM binding task accounted for the largest proportion of variance between AD and non-AD groups and held the greatest classification power to identify patients with AD. STM conjunctive binding places little demands on executive

functions and appears to be subserved by components of the memory network which are targeted by AD, but not by non-AD dementias.

Introduction

Binding is a cognitive function responsible for integrating the multiple features that make up complex stimuli or the different events comprised by rich experiences (Treisman, 2006; Zimmer, Mecklinger, & Lindenberger, 2006). In memory, binding ensures an accurate representation and retention of the *relation* between items (e.g., names and faces) or the *conjunction* of features into objects (e.g., shapes and colours). Relational and conjunctive binding functions operate both in short-term memory (Piekema, Kessels, Mars, Petersson, & Fernandez, 2006; Piekema, Kessels, Rijpkema, & Fernandez, 2009; Piekema, Rijpkema, Fernandez, & Kessels, 2010) and in long-term memory (Moses & Ryan, 2006) and they are all affected by Alzheimer's disease (AD) (Gallo, Sullivan, Daffner, Schacter, & Budson, 2004; Granholm & Butters, 1988; O'Connell et al., 2004; Parra et al., 2009a; 2010a; 2011; Swainson et al., 2001). However, conjunctive binding in STM appears to be the only memory binding function that is specifically affected by AD relative to healthy ageing or other age-related conditions such as chronic depression (Brockmole, Parra, Della Sala, & Logie, 2008; Brown & Brockmole, 2010; Parra, Abrahams, Logie, & Della Sala, 2009b; Parra,

Abrahams, Logie, & Della Sala, 2010b). It is as yet unknown whether this specificity holds true across other non-AD dementias.

Memory binding in ageing and dementia

Relational binding in long-term memory has been thoroughly investigated in AD (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; Lowndes & Savage, 2007; O'Connell et al., 2004; Swainson et al., 2001). One example is associative learning, a function responsible for the long-term retention of the relation between different pieces of information such as objects and their locations, names and faces, etc (Granholm & Butters, 1988; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Lindeboom et al., 2002; Swainson et al., 2001). Associative learning also declines in healthy ageing (de Jager, Blackwell, Budge, & Sahakian, 2005; de Jager, Milwain, & Budge, 2002; Naveh-Benjamin, 2000; Naveh-Benjamin, Brav, & Levy, 2007; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; O'Connell et al., 2004; Old & Naveh-Benjamin, 2008) and has been found to be impaired in other forms of non-AD dementia such as Vascular dementia (Clague, Dudas, Thompson, Graham, & Hodges, 2005), Fronto-Temporal dementia (Dimitrov et al., 1999) and Parkinson's dementia (Taylor, Saint-Cyr, & Lang, 1990). Associative learning is therefore sensitive but not specific to AD. In terms of the neural underpinnings, associative learning appears to require the integrity of a functional network including the hippocampus which is affected in ageing and in AD (Grady, 1998; 2008; Grady &

Craik, 2000). However damage to components of the network other than the hippocampus (i.e., prefrontal cortex) has been proposed to account for poor performance in non-AD dementias (Dimitrov et al., 1999; Giovannetti et al., 2001; Taylor et al., 1990). Moreover, relational binding in STM, a function which is also affected in healthy ageing (Mitchell, Johnson, Raye, & D'Esposito, 2000; Mitchell, Raye, Johnson, & Greene, 2006), appears to rely on a similar hippocampal network (Piekema et al., 2006; 2009; 2010).

Conjunctive binding is a memory function different from that involved in learning the relation between features, i.e., associative learning (for a review see Moses & Ryan, 2006). STM binding tasks which assess the ability to retain conjunctions of features such as shapes and colours have been used to investigate the representation format used to retain complex stimuli (e.g., Vogel, Woodman, & Luck, 2001; Wheeler & Treisman, 2002). Whereas associative memory is responsible for forming complex representations by linking events or items each of which retains their own identity, conjunctive binding leads to the *integration* of features within objects and formation of a new identity. Moreover, unlike associative memory, STM binding appears to be sensitive to AD (Parra et al., 2009a; 2010a & b; 2011) but age insensitive (Brockmole et al., 2008; Brown & Brockmole, 2010; Cowan, Naveh-Benjamin, Kilb, & Sauls, 2006; Mitchell et al., 2000; Parra et al., 2009b). Evidence from studies with patients with focal hippocampal lesions and from functional neuroimaging studies suggests that STM conjunctive binding is not

dependent on the integrity of the hippocampus (Baddeley, Allen, & Vargha-Khadem, 2010; Baddeley, Jarrold, & Vargha-Khadem, 2011; Piekema et al., 2010) but on structures which appear to be either unaffected or reorganised in healthy ageing (Grady, 1998; 2008; Insausti et al., 1998).

STM binding has proved sensitive to the effects of sporadic (Parra et al., 2009a; 2010b; 2011) and familial AD (Parra et al., 2010a; 2011). Moreover, STM binding is the only cognitive function which has been found to be impaired in otherwise completely asymptomatic carriers of the Preseniline-1 mutation E280A more than 10 years before the average age of onset of the disease (Parra et al., 2010a; 2011). The present study aimed at investigating whether STM binding impairment is specific to AD.

Methods

Participants

Five groups of patients with dementia and a healthy control group were recruited for the study. Standard diagnostic criteria were used to identify patients with AD (n = 15; 6 with mild and 9 with moderate dementia- Haxby, Raffaele, Gillette, Schapiro, & Rapoport, 1992) (DSM-IV-TR and the NINCDS-ADRDA, McKhann et al., 1984), Frontotemporal dementia (FTD) (n = 17; 13 mild and 4 moderate dementia) (Neary et al., 1998), dementia associated with Parkinson's Disease (PD) (n = 14; 11 mild and

3 moderate dementia) (Emre et al., 2007), Vascular dementia (VasD) (n = 14; 9 mild and 5 moderate dementia) (Roman et al., 1993) and dementia with Lewy bodies (DLB) (n = 10; 3 mild and 7 moderate dementia) (McKeith et al., 1996). Healthy controls (n = 20) were relatives of patients or members of the Hospital staff who did not report any current health problems or significant clinical history. Participants were screened for colour vision as assessed by the test of Colour Blindness (Dvorine, 1963). All participants gave their signed consent to take part in this study. The demographic, global cognitive and functional profiles are shown in Table 1. One-way ANOVA with these variables revealed no significant differences across groups in any of the contrasts performed (Bonferroni-corrected, alpha sets to 0.001).

----- Insert Table 1 about here -----

Assessment

Neuropsychology

The neuropsychological battery comprised tests of global cognitive functioning (MMSE, -Folstein, Folstein, & McHugh, 1975), pre-morbid intelligence (Wechsler Test of Adult Reading – WTAR, Wechsler, 2001) and current cognitive assessment including logical thinking (Raven's Progressive Matrices, Raven, Raven, & Court, 2003), memory (Prose Memory, Spinnler & Tognoni, 1987, and Digit Span forward), visuo-spatial functions (Visual Object and Space Perception Battery- Warrington &

James, 1991), attention and executive functions (Trail Making Test - Reitan, 1958, Semantic Verbal Fluency, - Spinnler & Tognoni, 1987).

STM binding task

The task presented visual arrays of stimuli which appeared simultaneously on the PC screen and remained for a total of 1.5 sec per feature (e.g., two coloured objects comprised 4 features and appeared for 6 sec). Healthy elderly were presented with arrays of 8 items in conditions assessing memory for single features and 4 items in the condition assessing the binding of these features in memory. Patients were presented with arrays of 4 items in conditions assessing memory for single features (i.e., common objects and colours) and of 2 items in the condition assessing the binding of these features in memory (i.e., coloured objects). Previous studies have showed that this procedure minimizes the differences between AD patients and controls on the single feature conditions whereas AD patients' performance on the binding condition drops dramatically (Parra et al., 2009a; Parra et al., 2010a & b; 2011). Keeping performance of patients and controls at a similar level on the conditions assessing STM for single features allowed us to rule out the contribution of task difficulty to performance. Moreover, this manipulation also allowed us to keep performance far from floor in patients and from ceiling in controls. Immediately after the study array (there was no delay), verbal recall was assessed by

asking participants to name aloud the items they had just seen in no particular order. The experimenter recorded their responses using a scoring sheet.

Four experimental conditions were used in the task. They were blocked and administered in a counterbalanced order. *Memory for colours*: the study array consisted of different coloured squares drawn from a set of 11 colours (Red, Blue, Green, Brown, Orange, Yellow, Purple, Gray, Turquoise, Pink, and Black). Only colour information was presented in this condition. *Memory for objects*: the study array consisted of common objects drawn from a set of 11 objects (Bed, Apple, Banana, Bell, Shoe, Car, Book, Chair, Cup, Guitar, and Button). Objects were outlines of figures. Only object information was presented in this condition. *Memory for objects and colours unbound*: In this condition colours and objects were presented simultaneously on the same array but they appeared as separate features. Half of the items were coloured squares and the other half were figure outlines of common objects. Participants were instructed as above, but they were told to remember as many objects and as many colours as possible. *Memory for Object-colour bindings*: In this condition the study array consisted of different objects filled with different colours. These coloured objects were constructed by randomly combining objects with colours from the two sets always avoiding typical associations (e.g. red apple). Participants were instructed to remember each object together with the colour in which it was presented.

Colours and objects were evenly distributed across the different experimental conditions. Individual or bound features could be repeated within conditions but not within a trial. Additionally, identical arrays were never repeated within any experimental condition.

Procedures

Participants were initially presented with two separate arrays: 20 colours and 20 objects. These arrays included the colours and objects to be presented in the STM task in addition to 9 other colours and 9 other objects intermixed within the arrays. Participants were requested to name the colours and the objects. All the participants recruited for the study correctly named all of the objects and all the colours selected for the experiment. The four conditions of the STM task were then administered. Each consisted of 6 trials which were fully randomized across participants.

Analyses

The neuropsychological scores were compared across groups using one-way ANOVA. To identify whether the selected groups differed in any of the neuropsychological functions assessed, Bonferroni-corrected post-hoc contrasts were performed (corrected alpha threshold set to 0.001). Performance on the STM task was analysed with a Mixed ANOVA Model. The between-subjects factor was Group (Controls vs. AD vs. FTD vs. PD vs. VasD vs. LBD) and the with-subjects factor was condition (Colour Only vs. Object Only vs. Objects and Colour Unbound vs. Object-Colour Binding). Post-hoc contrasts were carried out to further assess significant main effects. Performance on the neuropsychological battery and on the STM binding task was further assessed with a Hierarchical Multiple Linear Regression Model aimed at identifying the proportion of variance accounted for by these

variables when patient groups were compared. Those variables that accounted for a significantly large proportion of variance were then used in a Discriminant Analysis which aimed at verifying the percentage of correct classification that could be achieved when the five groups of patients along with sensitive measures entered the model. This would indicate which neuropsychological functions could better assist in the differential diagnosis of AD from non-AD dementias.

Results

Analysis of variance

Neuropsychology

The mean scores of the neuropsychological tests for each group as well as the cut-off scores drawn from the literature are shown in Table 2. The mean scores for all the patient groups were below cut-off on the Object Decision subtest of VOSP battery. AD patients performed below cut-off on the Prose Memory test. AD and DLB patients performed slower than cut-off in the TMT test. Patients with DLB were impaired in the Raven Matrices test and in the Verbal Fluency test. Patients with FTD and VasD also showed impairment in the Verbal Fluency test.

When patients' performance was entered in a one-way ANOVA, the results showed significant main effects ($p < 0.05$) for all the tests apart from Digit Span.

Bonferroni-corrected post-hoc contrasts were then carried out (with alpha corrected

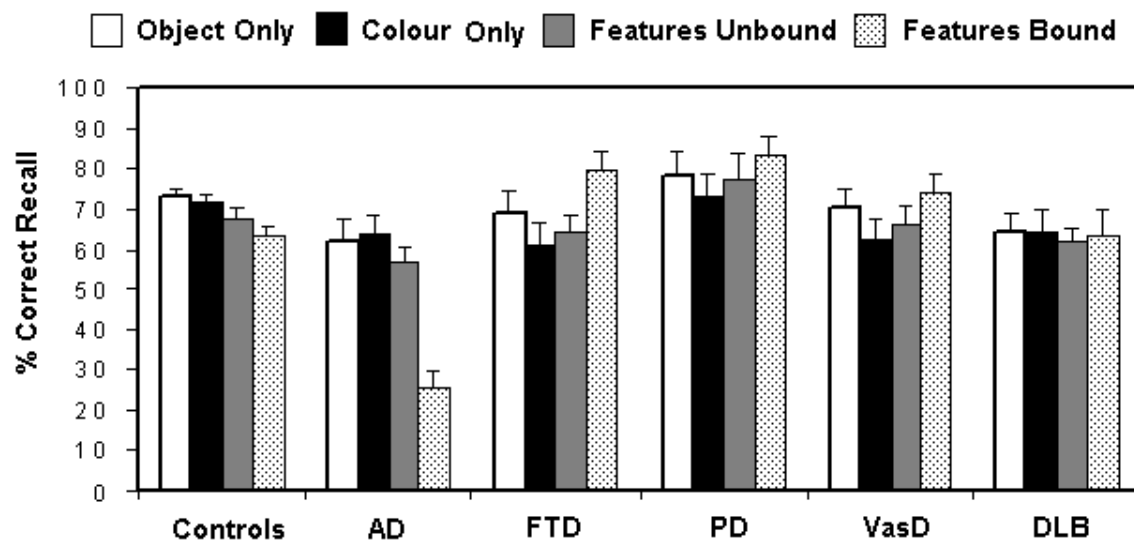
at 0.001). These contrasts showed that patients with AD had significantly poorer performance than PD and VasD patients on the Prose Memory test. DLB patients were slower than patients with FTD and PD in the TMT. No other contrast reached the significance threshold.

----- Insert Table 2 about here -----

STM binding task

Mean performance on the STM binding task is shown in Figure 1. The mixed ANOVA revealed a significant main effect of Group [$F(5,84) = 5.60$, $p < 0.001$] whereby AD patients performed more poorly than the other groups except than the DLB group [AD vs. Controls: Mean Difference (MD) = 16.91, $p < 0.01$; AD vs. FTD: MD = 16.51, $p < 0.05$; AD vs. PD: MD = 25.97, $p < 0.001$; AD vs. VasD: MD = 16.16, $p < 0.05$ and AD vs. DLB: MD = 11.33, n.s.]. Contrasts carried out across the other groups did not show significant effects. The effect of Condition fell short of significance [$F(3,252) = 2.15$, $p = 0.094$]. However, the interaction between Group and Condition was significant [$F(15,252) = 7.9$, $p < 0.001$].

Bonferroni-corrected post-hoc contrasts revealed that the interaction was solely driven by AD patients' performing more poorly than the other five groups only in the object-colour memory binding condition (see Supplementary Table S1). No other contrast performed across groups or across conditions was significant.



----- Insert Figure 1 about here -----

Regression analysis

The post-hoc tests with standard neuropsychological scores showed that the Prose Recall task differentiated between AD, PD and VasD patients but not between AD, FTD and DLB patients. This contrasts with the finding that the AD group performed worse than all the other non-AD groups on the Features Bound condition of the STM binding task. We considered it important to investigate the proportion of variance that could be accounted for when the most sensitive standard test and the novel STM binding task are used together in the assessment. This would shed additional light into the specificity of the STM binding deficits in AD.

The outcome from the regression analysis is presented in Table 3. Five tests accounted for significant between-group variability. The Prose Recall task accounted for a significant proportion of variance between AD and all the other non-AD

groups. Raven Matrices scores differentiated AD from FTD and PD, with AD patients performing worst. The TMT (B-A) differentiated AD from FTD, VasD and PD; LBD patients were the slowest group. The Verbal Fluency task was able to differentiate AD from FTD and LBD, with the last two groups showing poorer performance than AD. The Features Bound condition of the STM binding task accounted for a significant proportion of variance between AD and all the other non-AD groups. The AD patients exhibited the worst performance on this task. Moreover, the amount of variance explained in group comparisons by this test was greater than that explained by the Prose Recall task. These results confirm that impairment in memory, attention, and executive functions is the most typical profile of AD. However, these results also suggest that by incorporating the STM binding task in the assessment, a better classification of AD relative to other types of dementia can be achieved.

----- Insert Table 3 about here -----

Discriminant and classification analysis

We finally investigated whether the classification power of the two tests that explained the largest proportion of variance in the previous analysis (i.e., Prose Memory and Features Bound condition of the STM binding task) could be improved when both are considered in the assessment model. To this end we defined three

models. Model 1 comprised the Prose Recall task. Model 2 comprised the Features Bound condition of the STM binding task. Model 3 incorporated both Model 1 and Model 2. We submitted these models to a discriminant analysis. Moreover, we calculated the percent of cases that fell below cut-off when Model 1 and 2 were considered separately. This would also be informative of the specificity of the two tasks in the assessment of AD and non-AD dementias.

----- Insert Table 4 about here -----

The discriminant analysis showed that with both models AD was the best classified group. Model 1 classified FTD and VasD patients better than Model 2. Model 2 achieved better classification for AD, PD, and DLB than Model 1 (Table 4). Overall the two models yielded similar percentage of grouped cases correctly classified. When both models were considered together (Model 3), the overall classification power increased and AD remained to be the best classified group. Further classification analysis using cut-off scores showed that both models had similar accuracy to identify impairments in non-AD patients [Positive Cases out 55: Model 1 = 7, Model 2 = 11; $\chi^2 = 1.06$, n.s.]. However, Model 2 identified impairments in AD cases significantly better than Model 1 [Positive Cases out 15: Model 1 = 10, Model 2 = 15; $\chi^2 = 6.0$, $p = 0.01$]. This confirms the observation that the Features Bound

condition of the STM binding task (Model 2) combines more sensitivity and specificity for AD than other more traditional neuropsychological measures.

Discussion

We investigated whether STM binding, a function which has proved to be impaired in AD (Parra et al., 2009a; 2010a & b; 2011) was also impaired in patients with non-AD dementia whose cognitive profiles overlap with that of AD patients. STM binding impairments were found to be specific to AD and were not observed in non-AD dementias. These results have important implications for our understanding of the cognitive and neural underpinning of memory binding and also for the assessment of dementia.

Memory deterioration in dementia

Although associative learning appears to deteriorate early in the course of AD and Associative Learning Tasks are regarded as sensitive measures of AD (Fowler, Saling, Conway, Semple, & Louis, 2002; Gallo et al., 2004; Lee et al., 2003; Lowndes & Savage, 2007; O'Connell et al., 2004; Swainson et al., 2001), these impairments do not seem to be a hallmark of the disease. Older adults who do not meet MCI or AD criteria can also show poor associative learning functions (de Jager et al., 2002; 2005; Lowndes et al., 2008; Naveh-Benjamin et al., 2007; Old & Naveh-Benjamin, 2008).

Associative Learning Tasks also fail to differentiate between patients with AD and those with LBD (Lindeboom et al., 2002) or FTD (Dimitrov et al., 1999; Lee et al., 2003). When the associative learning task involves spatial information such as object-location (e.g., PAL-CANTAB), performance of patients with PD may also be impaired (Brandt, Shpritz, Munro, Marsh, & Rosenblatt, 2005; Sahakian et al., 1988; Taylor et al., 1990). Moreover, currently available episodic memory tests (including Associative Learning tasks) show practice effects when they are used for follow up purposes (Rabbitt, Diggle, Holland, & McInnes, 2004; Rabbitt, Lunn, Ibrahim, & McInnes, 2009; Rabbitt, Lunn, Wong, & Cobain, 2008) and performance on these tests quickly reaches floor levels even in the initial stages of dementia (Frisoni, Fox, Jack, Jr., Scheltens, & Thompson, 2010; Locascio, Growdon, & Corkin, 1995; Spinnler & Della, 1988; Welsh, Butters, Hughes, Mohs, & Heyman, 1991; Welsh, 1991; Welsh, Butters, Hughes, Mohs, & Heyman, 1992).

As a caveat it could be argued that the task we used, despite seemingly a STM binding task, might be sensitive to LTM deficits. Recent studies have shown that patients with hippocampal lesions show impairments even in tasks with minimal delay (Konkel, Warren, Duff, Tranel, & Cohen, 2008; Warren, Duff, Tranel, & Cohen, 2011). Therefore, the performance difference between AD patients and the other groups could be accounted for by a deficit in hippocampus-supported LTM retrieval mechanism (Hannula, Tranel, & Cohen, 2006; Ryan & Cohen, 2004) present in AD but affecting the other dementias to a lesser extent. However, this intriguing,

alternative account seems improbable.. In the present manuscript we have capitalised on the distinction between relational (hippocampal-sensitive) and conjunctive (hippocampal-insensitive) binding mechanisms and the contribution that their impairment might make to memory binding deficits in AD. In fact, in the studies in which no delay was used (i.e., Warren et al., 2011) some form of relational representation was required; for instance, linking items to spatial representations. To avoid such relational mechanism, in our conjunctive memory binding task spatial information was made uninformative. Under these conditions, it is thought that the hippocampus does not support performance as demonstrated by studies with patients with damage to MTL structures (Baddeley et al., 2010; 2011) or with healthy individuals (Piekema et al., 2010).

Relational binding operates both in LTM and in working memory or STM and appears to rely on similar mechanisms in both types of memory process. For example, like LTM studies (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Montaldi, & Migo, 2007; Mayes et al., 2004; Moses & Ryan, 2006) those involving the processing of object-location bindings in working memory have also reported activation of the MTL-fronto-parietal network (Piekema et al., 2006; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000) and poor performance in healthy older adults (Mitchell et al., 2000; 2006) as well as in amnesic patients (Hannula et al., 2006; Olson, Moore, Stark, & Chatterjee, 2006; Ryan & Cohen, 2004; Warren et al., 2011).

Conjunctive binding appears to support the integration of features within objects (e.g., intra-item binding). This type of binding serves as a basis for object identity (i.e., Gestalt features such as shape and colour) and seems to occur via brain mechanisms different to those subserving the *processing* of relational information (Mayes et al., 2004; 2007; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Moses & Ryan, 2006; Piekema et al., 2006; Rama et al., 2004; Sala & Courtney, 2007). This type of memory processing may not involve the same MTL-fronto-parietal network required to process relational representations such as object-location bindings in working memory (Prabhakaran et al., 2000).

Processing integrated features into single object representations in working memory may rely on components of the MTL-fronto-parietal network which are more severely impaired in AD relatively to other non-AD dementias. Potential candidates include the extrahippocampal regions (i.e., entorhinal or perirhinal cortices) which may be an important component of the network responsible for processing novel associations which are encoded in a unitized manner (i.e., objects) (Haskins, Yonelinas, Quamme, & Ranganath, 2008). These regions deteriorate early in AD (Juottonen et al., 1998; Juottonen, Laakso, Partanen, & Soininen, 1999) but to a lesser extent in non-AD dementias (Du et al., 2002; Frisoni et al., 1999; Laakso et al., 1996; Tam, Burton, McKeith, Burn, & O'Brien, 2005).

Neuropsychological assessment of dementia

The results presented here support the validity of the STM binding task in the assessment of AD. The present study documents, for the first time, the specificity of this novel task in assessing AD among common forms of dementia. The usefulness of the STM binding task in the differential diagnosis between AD and other non-AD dementias was assessed against other standard neuropsychological tasks which were less able to differentiate between the dementias.

It is worth noting that 6 AD patients were in the mild stages of the disease whereas 9 were in the moderate stages and all showed STM binding deficits. Together with previous reports of STM binding deficits in preclinical AD (Parra et al., 2010a; 2011b), this evidence suggests that STM binding deficits appear early in the course of the disease and that this task could potentially assist in its diagnosis.

Background assessment showed that 67% of the AD patients were impaired on the Prose Memory test. In contrast 100% were impaired on the STM binding task. Moreover, 67% of these patients had attention (TMT) problems, 40% of them presented with executive impairments (Verbal Fluency) and 67% performed below cut-off in the object decision subtest of the VOSP. The results indicate that two thirds of the AD patients had a predominant amnesic profile, but that STM binding deficits were found in all patients with AD irrespective of their neuropsychological profile. Taken together the results from this study showed that the Prose Memory test and the Features Bound condition of the STM binding task were the two tests that accounted for the largest proportion of variance between AD and all the other

non-AD groups. However, the amount of variance explained by the Features Bound condition of the STM binding task was the largest and this was the only test on which 100% of the AD patients performed below cut-off. This suggests that the Features Bound condition of the STM binding task combines both sensitivity and specificity in the assessment of AD. In fact, the Discriminant analysis showed that the STM binding task alone could classify AD patients better than any of the other tasks used in the assessment. These are novel findings in a relatively small sample of patients. Whether this will hold true for larger samples of patients is an issue that requires further investigation. Until then, STM binding tasks could be used alongside other standard tests of neuropsychological functions which have proved useful in the assessment of dementia.

Previous studies showed that STM binding is not affected by age (Brockmole et al., 2008; Brown & Brockmole, 2010; Parra et al., 2009b). Moreover, using visual STM binding tasks we have documented the validity of this paradigm to differentiate between patients with AD and healthy volunteers or elderly with chronic depression (Parra et al., 2010b). A study investigating STM binding functions in early-onset familial AD found that asymptomatic carriers of the mutation E280A of the Presenilin-1 gene (Lopera et al., 1997) who performed within the normal limits in an extensive neuropsychological battery, showed specific deficits in this function more than 10 years before the average age of onset of dementia (Parra et al., 2010a; 2011). In fact, STM binding deficits were observed in

carriers whose performance on the Paired Associated Learning task of the Wechsler Memory Scale (Wechsler, 1945) was normal. This supports the segregated nature of these memory processes and suggests a differential vulnerability of associative learning and STM binding to AD.

In contrast to other forms of short term and long term memory binding, STM conjunctive binding appears to be uniquely specific to AD and not affected by age, depression or other non-AD dementias. It appears to depend on parts of the MTL-frontoparietal network other than the hippocampus, but more severely affected by AD than other dementias, the most likely candidate being extrahippocampal regions. The task also provides a promising tool to be used in clinical settings for the assessment of dementia.

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Table 1. Demographic, global cognitive and functional measures for the six groups of participants.

	Controls (n = 20)		AD (n = 15)		FTD (n = 17)		PD (n = 14)		VasD (n = 14)		DLB (n = 10)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	69.35 (6.21)	(61-82)	72.93 (5.79)	(60-80)	69.12 (3.90)	(60-75)	70.00 (8.39)	(60-84)	73.36 (7.16)	(60-81)	72.90 (6.85)	(62-82)
Education	7.25 (2.97)	(5-13)	7.13 (3.74)	(2-17)	7.71 (4.40)	(5-17)	6.71 (3.07)	(4-13)	7.29 (4.86)	(2-17)	6.70 (4.40)	(3-13)
MMSE			19.87 (3.56)	(16-25)	23.35 (4.81)	(12-29)	23.71 (3.60)	(16-27)	22.50 (2.47)	(18-26)	19.80 (4.49)	(14-27)
VIQ			93.51 (4.66)	(86-102)	94.39 (12.03)	(75-114)	94.95 (10.97)	(81-111)	96.48 (9.79)	(83-116)	87.79 (13.08)	(75-112)
GDS			5.60 (0.51)	(5-6)	2.59 (3.99)	(0-10)	2.71 (4.81)	(0-12)	1.64 (3.63)	(0-10)	1.50 (3.57)	(0-11)
IADL			5.13 (1.41)	(3-7)	4.65 (1.50)	(2-8)	4.43 (1.40)	(1-6)	4.29 (2.09)	(1-8)	3.40 (2.72)	(0-7)

GDS : Geriatric Depression Scale (Yesavage et al., 1982); IADL : Instrumental Activities of Daily Living (Lawton & Brody, 1969);

MMSE: Mini-Mental State Examination (Folstein et al., 1975); VIQ : Verbal IQ as determined by the WTAR (Wechsler, 2001).

Table 2. Mean scores for the neuropsychological tests used with the different groups of patients with dementia.

	Cut-off (*)	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	VasD		DLB	
								Mean (SD)	Range	Mean (SD)	Range
Prose Memory (Total Recall) Score range: 0-16	4.5 ¥	3.44 (2.18)	(0-6.3)	8.20 (4.18)	(0-14.6)	10.59 (3.36)	(0-13.5)	10.41 (2.0)	(7-13.5)	8.65 (4.67)	(2-14.6)
Digit Span Score range: 2-9	2.75 ¥	4.20 (0.94)	(3-6)	3.94 (1.03)	(2-6)	4.71 (0.99)	(3-6)	4.14 (0.53)	(3-5)	4.20 (1.03)	(3-6)
VOSP Score range: 0-20	14	12.40 (3.38)	(2-16)	12.12 (3.50)	(5-18)	13.79 (2.61)	(10-20)	12.00 (3.80)	(1-16)	9.10 (3.41)	(5-16)
Raven Matrices Score range: 0-48	14.75 ¥	17.73 (4.86)	(6-24)	22.35 (5.99)	(7-32)	22.86 (4.38)	(14-29)	19.71 (3.85)	(13-26)	14.50 (6.75)	(8-29)
TMT (B-A) Score range: 0-inf	185 ¥	250.93 (109.14)	(102-464)	128.35 (83.52)	(36-370)	113.64 (49.65)	(57-255)	139.71 (64.51)	(85-276)	290.60 (126.42)	(70-460)
Verbal Fluency Score range: 0-inf	9.0 ¥	12.60 (6.10)	(4-25)	7.47 (2.53)	(4-11)	11.07 (2.92)	(5-15)	9.29 (2.09)	(7-13)	8.10 (2.73)	(5-15)

(*) Digit Span Forward (Orsini et al., 1987); Prose Memory (Total Recall) (Spinnler & Tognoni, 1987); Raven Matrices (Raven et al., 2003); TMT (B-A) (Giovagnoli et al., 1996); Verbal Fluency (Semantic categories) (Spinnler & Tognoni, 1987); VOSP (Object decision) (Warrington & James, 1991); ¥ = lower bound (5%) of the population distribution (Spinnler & Tognoni, 1987).

Table 3. Results of the regression analysis with the standard neuropsychological and STM scores in the five groups of patients.

	AD vs. FTD		AD vs. PD		AD vs. VasD		AD vs. DLB		Total		
	R (%)	P-value	R (%)	P-value	R (%)	P-value	R (%)	P-value	Cum R (%)	F	P-value
Prose Memory (Total Recall)	32.10	< 0.001	62.0	< 0.001	73.8	< 0.001	35.5	0.001	19.8	18.0	<0.001
Digit Span Forward	0.15	0.466	3.60	0.164	3.60	0.884	0.40	1.000	18.7	8.94	<0.001
VOSP (Object decision)	0.30	0.818	1.80	0.229	3.40	0.766	16.30	0.026	31.0	11.33	<0.001
Raven Matrices	13.00	0.024	21.90	0.006	1.60	0.237	3.80	0.176	37.4	11.31	<0.001
TMT (B-A)	27.70	0.001	40.70	< 0.001	26.20	0.003	0.10	0.412	36.6	8.96	<0.001
Verbal Fluency (Semantic Categories)	22.70	0.003	1.00	0.400	8.80	0.065	13.50	0.040	37.3	7.85	<0.001
Features Unbound	0.13	0.246	19.20	0.010	4.10	0.149	0.10	0.427	37.6	6.93	<0.001
Features Bound	72.70	< 0.001	77.90	< 0.001	70.50	< 0.001	53.90	< 0.001	42.2	7.31	<0.001

Table 4. Results of the discriminant and classification analyses for each model across the five groups of patients.

		AD	FTD	PD	VasD	DLB	% Grouped cases correctly classified
Model 1	Count	11	3	9	4	0	38.6
	% M	73.3	17.6	64.3	28.6	0	
	% C	66.7	23.5	7.1	0.0	20.0	
Model 2	Count	13	0	11	0	4	40.0
	% M	86.7	0	78.6	0	40.0	
	% C	100	17.6	14.3	14.3	40.0	
Model 3	Count	14	6	10	5	2	52.9
	% M	93.3	35.3	71.1	35.7	20.0	

Model 1 = Prose Memory Test; Model 2 = Features Bound condition of the STM

binding task; Model 3 = Model 1 + Model 2; % M = percentage of cases correctly

classified by the model within each group; % C = percentage of cases that fell below

cut-off with the model.

Figure Captions

Figure 1. Mean scores obtained in the six assessed groups with the STM task (error bars represent the standard error of the mean).